PATENT SPECIFICATION 1,008,193

DRAWINGS ATTACHED.

1,008,193

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Int. Cl.:—A 61 f 1/00 //D 01 d, f, D 03 d, D 04 b, c, d.

COMPLETE SPECIFICATION.

Improvements in or relating to Surgical Implants.

We, ETHICON, INC., a Corporation of the State of New Jersey, United States of America, located at Somerville, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to reinforced collagen prostheses to be placed in the human body, and to a method of making the same. More particularly, this invention relates to collagen articles that are reinforced with non-absorbable fabrics.

In the surgical repair of hernias, tantalum gauze and inert fabrics have found considerable use, particularly in older patients who are recognized to have a reduced ability to rebuild tissue at the point of surgery. Tantalum gauze, however, has the undesirable property of work hardening and may curl up within the body, causing discomfort. Inert fabric prostheses have the disadvantage that they do not become a part of the body tissues. Such inserts frequently remain surrounded by a pool of sera after the healing process. A suitable prosteses for strengthening the repair should be non-toxic, flexible and porous. The ideal prostheses should retain its strength permanently in intimate contact with body fluids and should be readily accepted and incorporated into the tissue. Porosity is an im- the healing process. A suitable prostheses to avoid the formation of fluid pockets and to promote the growth through the fabric of repair tissue.

The present invention has for its principal object the provision of flexible films and tubes constructed of collagen and reinforced with an open mesh, non-absorbable fabric that is compatible with the human body.

A further object of the invention is the provision of such flexible tubes, that are not subject to kinking or collapsing, in any desired diameter or length suitable for use with human arteries or veins.

Another object is the manufacture of prostheses having a structure which promotes the growth of body tissue into and through the prostheses during the healing process.

It has now been discovered that an improved prostheses can be constructed using as a framework or support a non-absorbable plastic material, knitted, woven or braided to have a wide mesh, thus permitting easy invasion by the host into the interstices between the non-absorbable fibers. In the improved prostheses of the present invention, the interstices between the non-absorbable fibers are initially filled and rendered blood tight by collagen fibrils. The collagen fibrils have considerable tensile strength, are non-antigenic, are slowly absorbed and permit satisfactory in-growth of fibroblasts and endothelial cells, resulting in attachment of the prosthesis to the host tissues, Since collagen is the type of connective tissue normally laid down by the body during the healing process, there is no appreciable decrease in the strength of the prosthesis during the period that the collagen fibrils are being replaced.

The invention will appear more clearly from the following detailed description when taken in connection with the accompanying drawings, showing by way of example, a preferred embodiment of the invention. Referring now to the drawings:

Figure 1 is a view of a reinforced collagen

[*Price*

film. In this view, the surface collagen films have been forcibly pulled away from the non-absorbable fabric to illustrate the laminated construction.

Figure 2 is a greatly enlarged view of the non-absorbable fabric that forms the reinforcing central element of the structure illustrated by Figure 1.

Figure 3 is a view of a fabric mesh tube reinforced with a plastic helix.

Figure 3*a* is a cross-section on the line 3*a* in Figure 3, and Figure 3*b* is a detail of Figure 3*a* on an enlarged scale.

Figure 4 is a view, partially in section, of a fabric mesh tube reinforced with plastic rings and coated with collagen fibrils.

Figure 5 is a view, partially in section, of a reinforced molded collagen tube.

The non-absorbable fabric that is used to reinforce the collagen prostheses of the present invention may be knit, woven, crocheted or braided in the desired shape of any synthetic or natural fibers that are compatible with the human body. Examples of suitable materials are VINYON-N, (the word VINYON is a Registered Trade Mark) a resin manufactured by the Carbide and Carbon Corporation by copolymerizing vinyl chloride and acrylonitrile; Nylon, a polyamide resin made by polymerization of the hexamethylene diamine salt of adipic acid; ORLON (Registered Trade Mark), a synthetic fiber made by the E. I. duPont de Nemours & Co., from polyacrylonitrile; DACRON (Registered Trade Mark), a synthetic fiber made by the E. I. duPont de Nemours & Co., from terephthalic acid and ethylene glycol; TEFLON (Registered Trade Mark), a tetrafluoroethylene polymer manufactured by the E. I. duPont de Nemours & Co.; cotton and silk. DACRON and TEFLON are particularly preferred because both have displayed excellent retention of tensile strength over long periods of time and both are essentially inert, TEFLON being slightly more inert and slightly stronger than DACRON.

The non-absorbable fabrics may be knitted, crocheted, woven or braided in the shape of the desired prosthesis, as a film, tube, Y-tube, etc. Optionally, a film of the fabric may be rolled or cut and sewed with suitable thread to form the desired shape. The fabric may be further strengthened by plastic rings as illustrated in Figure 4. It is important that the mesh of the non-absorbable fabric be sufficiently open to permit the collagen fibrils to extend into and through the interstices of the fabric. These collagen fibrils that pass through the fabric cohere to the collagen fibrils on either side of the fabric framework and form a unitary structure that resists delamination.

After the fabric framework has been constructed in the desired shape, it is coated on both sides with a collagen mass obtained by swelling collagen fibrils in an aqueous acid solution. The swollen collagen fibrils are then frozen in position and shrunk by dehydration in an organic solvent.

The improved prostheses of the present invention may also be manufactured by an alternate process consisting of knitting, weaving, crocheting or braiding together an inert non-absorbable thread or yarn with collagen yarn or collagen multifilament. A suitable fabric can be woven with warp yarns of DACRON or TEFLON and filling yarns of collagen. The preparation of a collagen multifilament suitable for such use is described in Patent Specification No. 915,066.

It will be understood that the collagen present in the prostheses of the present invention may be treated with tanning agents such as formaldehyde, pyrogallol, chromium, etc., by methods well known in the art to obtain increased strength and control the rate at which the collagen will be absorbed.

The present invention is more fully described and exemplified in the following examples. Throughout the Specification and the Examples which follow, all quantities are expressed in parts by weight.

Example I

The deep flexor tendon of cattle is cleaned of fat, superficial non-collagenous protein and other extraneous matter and is sliced on an electric meat-slicing machine (rotary knife) in the frozen condition. The tendon sections are sliced perpendicularly to their longitudinal axis to a thickness of about 11 mils. In an analized aliquot sample of the tendon slices the dry solids amounted to 36.97%.

The sliced tendon is next treated with an enzyme solution to dissolve elastin. The enzyme solution is prepared by dissolving 0.15 part of ficin and 3.75 parts of ethylene diamine tetrasodium tetraacetate in 750 parts of water. Seventy-five parts of the sliced tendon is immersed in this solution which is stored at room temperature overnight. Then 2.25 parts of 30% hydrogen peroxide is added to destroy any residual ficin.

To this mixture of tendon slices in about 750 parts of water is added an additional 2244 parts of water and 5.87 parts of cyanoacetic acid. The swelling solution is cooled to below 25°C. This mixture is stirred in a dispersion kettle at about 60 r.p.m. The remaining steps in the process are carried out at temperatures below about 25°C. and the temperature of the collagen dispersion is not allowed to exceed this temperature.

Stirring is continued for about 3 hours, during which time the individual collagen slices are swollen. The dispersion is then homogenized by repeated passes through series-connected jets having orifices of 50 mils and 40 mils respectively. The dis-

persion is then forced through a leaf filter containing three screens of stainless steel containing 18% chromium and 8% nickel. These screens are separated by 1/8-inch spacers and decrease in mesh size so that the dispersion first passes a 14-mil screen, then a 9-mil screen, and finally a 4-mil screen. The dispersion of swollen collagen fibrils so obtained analyzes 1.09% solids and has a pH of 2.52.

The above collagen dispersion (300 grams) is poured into a stainless-steel tray measuring 15"×1-1/2" and smoothed out. A DACRON tulle is placed flat on the surface of the collagen dispersion and covered with another 300 grams of collagen dispersion. The tray is frozen in a sub-zero cabinet at −20°C. overnight. The frozen sandwich is then removed from the tray and immersed in a circulating bath containing 5 liters of 99% isopropranol and 25 milliliters of concentrated ammonium hydroxide at room temperature. After approximately four hours, the isopropanol solution is replaced with 5 liters of a fresh solution and the dehydration is continued overnight at room temperature. The isopropanol solution containing the water extracted is removed and a third bath of 99% isopropanol is used in the further dehydration of the collagen. The third bath is replaced in turn with a fourth bath of 99% isopropanol containing 0.4% formaldehyde, the dehydrating time amounting to 6 to 8 hours in both the third and fourth baths. At this time, the collagen fibrils are practically free of water and the DACRON-collagen film may be squeezed repeatedly between rubber rollers and air-dried in an oven at 45°C. overnight without damage.

The product so obtained is illustrated in Figure 1. The collagen fibrils of the surface coatings 11 and 12 extend through the openings 13 in the fabric 14 (Figure 2) and make is difficult to separate the collagen layer from the fabric.

Example II

A collagen dispersion is prepared according to the general procedure described in Example I above from 391 parts of sliced beef leg tendon and 17,110 parts of distilled water containing 7.3 parts of glacial acetic acid. This dispersion contains 0.8% solids and is placed in trays and reinforced by immersing a TEFLON fabric in the dispersion so that the fabric is suspended about halfway between the surface of the dispersion and the bottom of the tray. The contents of each tray is frozen and transferred in the frozen condition to a wire mesh frame. The frozen mass from each tray is dehydrated and coagulated by immersing in a circulating bath containing 60,000 parts of 99% isopropanol, 300 parts of concentrated ammonium hydroxide and 240 parts of formaldehyde (37% solution) at room temperature for approximately 8 hours. The circulating isopropanol bath is then replaced with a freshly constituted bath and the dehydration is continued overnight. This second bath is replaced with a third bath containing 99% isopropanol at room temperature and the dehydration is continued for 8 to 16 hours after which a fourth bath consisting of 99% isopropanol is substituted for the third bath. After dehydration for 8 to 16 hours in the fourth bath, the collagen coated TEFLON fabric is compressed at about 128 pounds per square inch pressure and air-dried at 50°C. overnight.

Example III

Example II above was repeated, substituting for the 7.3 parts of glacial acetic acid employed in that example 59.5 parts of cyanoacetic acid. The resulting prosthesis is sterilized by electron beam irradiation and may be used by the surgeon for hernia repair.

Example IV

A collagen dispersion is prepared according to the general procedure described in Example I above from 216 parts of sliced beef leg tendon and 9,780 parts of distilled water containing 50 parts of malonic acid. This dispersion contains 0.8% solids and is used to coat both sides of a TEFLON net fabric as described in Example I. The TEFLON-collagen composition is frozen and transfered in the frozen condition to a wire mesh frame. The frozen mass is dehydrated and coagulated by immersing in a circulating bath containing 45,000 parts of 99% isopropanol and 1330 parts of concentrated ammonium hydroxide at room temperature for approximately 8 hours. The circulating isopropanol bath is then replaced with a freshly constituted bath and the dehydration is continued overnight. This second bath is replaced with a third bath containing 99% isopropanol at room temperature and the dehydration is continued for 8 to 16 hours after which a fourth bath consisting of 99% isopropanol is substituted for the third bath. After dehydration in the fourth bath for 8 to 16 hours, the resulting product is air-dried at 50°C overnight.

The film so obtained is tanned by immersing for 30 seconds in a solution of 0.4 part of pyrogallol, 0.1 part tetrasodium ethylenediamine tetraacetic acid and 99.5 parts of water adjusted to pH 8.3 with ammonium hydroxide and redried in an oven at 50°C. for 6 hours.

The film is next immersed for 30 seconds in a solution of chromium (III) sulfate wherein the chromium is present as chromic oxide and which also contains minor amounts of lactoc acid and formaldehyde and which solution is adjusted to a pH of 2.7 with

sodium hydroxide, and dried in an oven at 50°C. overnight.

EXAMPLE V

A glass tube having an inside diameter of about 3/4 inch is fitted with a one-hole stopper of rubber through which a 5/16-inch glass rod is placed so that the glass rod extends coaxially within the glass tube. Before placing the glass rod and rubber stopper in position, the glass rod is covered with a piece of rubber tubing and a cylindrical tube of open-mesh woven DACRON about 5/8 inch in diameter is slipped over the glass rod and rubber tube. The glass tube and glass rod are assembled in an upright position with the bottom of the DACRON fabric tube resting on the rubber stopper. A dispersion of swollen collagen fibrils (0.08% collagen in 0.05 N acetic acid) is poured into the glass tube while maintaining the fabric tube in a coaxial position and equally spaced between the rubber tube and glass tube so that both sides of the fabric are coated with the collagen dispersion. This mold with the dispersion and fabric in place is then frozen in the vertical position for at least 4 hours at −20°C.

The mold is then placed in a static coagulation bath consisting of 2 liters of isopropanol alcohol, 30 cubic centimeters of concentrated ammonia (25%) and 10 cubic centimeters of formaldehyde (37% solution) at room temperature and the mold is maintained in the solution for 16 hours. The glass rod covered with the rubber tube and the formed collagen tube is then removed and placed in a dehydrating bath consisting of 2 liters of isopropanol alcohol. The collagen tube is left in this bath for an additional 16 hours to complete the dehydration.

After dehydration, the rubber tube with the collagen tube on it, is very carefully slid off the glass rod and the rubber tube is removed from the interior of the collagen tube by pulling on both ends of the rubber tube, thereby stretching the rubber tube and reducing its diameter. After the collagen tube is removed from the rubber tubing, it is plasticized in a bath consisting of 2 liters of 90% isopropanol alcohol (10% water) containing 5% glycerine. This plasticizing operation is optional. After 24 hours in the plasticizing bath, the collagen tube is supported on a glass rod and air-dried. The resulting product is illustrated in Figure 5 wherein the DACRON fabric tube 14 is coated on both sides by layers of collagen fibrils 11 and 12.

EXAMPLE VI

Tanned DACRON reinforced collagen films prepared by the method described in Example II above are rolled and sewed to form tubes about 1 centimeter in diameter and sterilized by irradiating with an electron beam. These tubes are used to replace segments of the abdominal aorta in mongrel dogs averaging 15 kilograms in weight. The animals were sacrificed at varying periods of time up to 8 months.

In general, the DACRON-collagen prosthesis shows an orderly pattern of organization at varying periods of time following insertion of the graft. The prostheses are all 5 centimeters long, divided into two types—thick and thin, according to the amount of impregnated collagen. No significant response difference can be detected in the two types. However, there is a significant difference, particularly in regard to initial hemorrhage, between collagen that has not been tanned and collagen that has been tanned. The following results are observed:

ONE WEEK

Gross Specimen: The one-week specimens are contained in a fibrous envelope which is not in any way adherent to the prosthesis. The intersices of the graft are still occluded by the impregnated collagen and the lumen is lined by a red, granular coagulum.

Microscopic Section: Sections of the proximal portion show an artefactual separation of the DACRON prosthesis from the surrounding fibro-adipose tissue forming the fibrous envelope of the graft.

The fibro-adipose tissue shows active fibroplasia and a minimal inflammatory infiltrate, comprised of polymorphonuclear leukocytes, a few lymphocytes and some plasma cells. The prosthesis itself shows the open meshwork of the DACRON fabric with the interstices filled by a series of haphazardly-arranged, tangled fibrils of bovine collagen with irregular interstices containing small number of erythrocytes. The outer surface of the prosthesis is covered by fibrin clot containing a few histiocytes, erythrocytes and neutrophils. There is no tongue-like extension of fibroplasia extending from the severed end of the aorta out into the graft, although there is a focal zone of reactive hyperplasia with capillaries and occasional inflammatory elements present at the anastomotic line. The lining consists of a thin fibrin layer, maximally 1 millimeter in thickness.

TWO WEEKS

Gross Specimen: By two weeks, the fibrous envelope is partially adherent but may be readily dissected free by lysis of delicate fibrous and fibrinous bands. The wall of the prosthesis and the lining are similar to those of the one-week specimen.

Microscopic Section: The two-week specimen shows a lack of inflammatory reaction similar to the specimen at one week.

The zone of fibrosis and fibroplasia in the fibro-adipose tissue adjoining the prosthesis is more mature, but as yet, there is no extension of fibroblasts into the prosthesis except at microscopic points. At the anastomosis, a well developed zone of fibroplasia extends across the anastomotic line onto the surface of the prosthesis and this tongue, in turn, is covered in part by endothelium. The prosthesis itself appears quite similar to the one-week specimen. The impregnated collagen appears well retained. The lining surface of the prosthesis now appears to be more dense fibrin with enmeshed erythrocytes and is somewhat thinner than the fibrin lining of the one-week specimen.

THREE WEEKS

Gross Specimen: At three weeks the fibrous envelope is more adherent than earlier, but still may be separated by forceful dissection. The lining is smoother and averages approximately one millimeter in thickness.

Microscopic Section: The peripheral enveloping zone of fibrosis is wider than previously and there is extension of fibroblasts into the interstices of the prosthesis at numerous points. Foreign body reaction to the DACRON of the prosthesis is present but still remains minimal. The inflammatory reaction is largely composed of histiocytes containing hemosiderin, plasma cells and lymphocytes. A mural fibrin thrombus is present and is focally organized, particularly at the anastomotic line. This organization is part of the tongue of advancing fibroblasts.

FOUR WEEKS

Gross Specimen: The four-week specimen is finely swedged to the fibrous envelope. A thin semi-transparent membrane covers the anastomotic lines.

Microscopic Section: A dense, surrounding fibrous envelope of mature collagenous connective tissue stains bright green in a Masson trichrome stain. The prosthesis adheres densely to this envelope and there are irregular extensions of this material into the interstitial areas of the prosthesis, most particularly between the DACRON meshwork. The interstices of the bovine collagen are now partially filled with green-staining collagenous connective tissue from the host. Inflammatory reaction is meager. The lining of the prosthesis consists of a zone of fibrous tissue apparently covered by endothelium that ranges in thickness from about 1 millimeter to less than 0.1 millimeter, being thinnest in its more central extent. This lining is continuous with the lining of the dog's aorta.

FIVE WEEKS

Gross Specimen: The five-week specimen is essentially the same as the four-week specimen.

Microscopic Section: The appearance is substantially the same as that of the four-week specimen, although there is slightly less of the bovine collagen remaining and more of green-staining collagen contributed by the host, particularly at the anastomosis.

TWO-AND-A-HALF MONTHS

Gross Specimen: The organization is almost complete. The fibrous envelope is firmly adherent and the lumen is lined by a thin, well-defined, smooth, semi-transparent grayish membrane.

Microscopic Section: There is notable progress of the fibrous tissue ingrowth into the prosthesis. Only an occasional, longitudinally, oriented fibre of collagen of the original prosthetic impregnation remains.

EIGHT MONTHS

Gross Specimen: The prosthesis is solidly united to the fibrous envelope. In cross section, the entire thickness of the grafted wall is slightly less than 2 millimeters. The lumen is covered by a smooth, glistening, grayish membrane that appears continuous with the intima of the host artery.

Microscopic Section: The prosthesis is completely organized by mature collagen that fills all of the interstices and has replaced all of the original bovine collagen fibrils except for a rare remaining fibril. The luminal aspect of the graft is smooth and is continuous with the dog's aorta. There is virtually no inflammatory reaction. The DACRON material of the prosthetic meshwork appears embedded in a continuous, rather uniform collagen mass. Externally, the graft blends with the adjoining fibro-adipose tissue.

EXAMPLE VII

A TEFLON fabric 14 is rolled to form a cylinder as indicated in Figure 3 and the fabric is sewed with DACRON thread 15 to a surrounding TEFLON helix 16 as best illustrated in Figures 3*a* and 3*b*. The supporting helix prevents the fabric tube from kinking or collapsing. This structure is covered with collagen fibrils on both sides by the procedure outlined in Example V. The resulting tube resists fraying at the ends and is adapted for use in grafts that traverse the inguinal fold or the popliteal space.

EXAMPLE VIII

A DACRON fabric 14 is sewed to form a cylinder as indicated in Figure 4 and the fabric is sewed with DACRON thread 15 to spaced surrounding TEFLON rings 17 as illustrated in Figure 4. The supporting rings 17 serve the same function as the helix 16 in Figure 3 and prevents the fabric tube from kinking or collapsing. This structure is

covered by collagen fibrils on both sides by the procedure outlined in Example V. The resulting article after electron beam sterilization is adapted for use in clinical vascular surgery. The finished tube is quite flexible and may be flexed repeatedly without collapsing.

EXAMPLE IX

A collagen dispersion (0.86% solids) is extruded into a circulating acetone dehydrating bath through a stainless steel spinnerette drilled with 192 openings arranged in concentric circles. Each opening in the spinnerette is approximately 18 mils in diameter and each opening has a 30° taper from this diameter at a point 34 mils from the spinnerette top surface to a 3/32 inch opening at the bottom surface of the spinnerette. The multifilament that emerges from the acetone dehydrating bath is wrapped 1-1/2 times around a godet and passes to a false twister. Warm air is circulated to dry out the multifilament as it contacts the false twister which is rotated at about 200 r.p.m. Under these conditions, the individual filaments that make up the multifilament do not bond together. The multifilament, which consists of 192 individual collagen threads, may be collected directly on a takeup spool.

The collagen multifilament so obtained may be woven together with non-absorbable multifilament or yarn such as DACRON yarn to make surgical prostheses in the form of fabrics and tubes. It is desirable that the collagen multifilament be tanned by methods well-known in the art to increase the strength and *in vivo* digestion time of the collagen. The collagen multifilament may be tanned prior to or after weaving. If the collagen multifilament is tanned prior to weaving, a collagen strand may conveniently be formed by twisting the collagen multifilament and drying under tension. Under these conditions, the individual filaments cohere to form a strand which may be woven into a fabric or tube with non-absorbable threads or yarn.

WHAT WE CLAIM IS:—

1 A device having the nature of a prosthesis to be placed in the human or animal body for surgical repair, comprising fabric non-absorbable by the body fluids and collagen fibrils.

2. A device according to claim 1 in which the fabric is impregnated with collagen fibrils.

3. A device according to claim 1 or 2 in which the interstices of the fabric are filled with collagen fibrils.

4. A device according to claim 1, 2 or 3 in which the fabric is coated on one side with collagen fibrils.

5. A device according to claim 4 in which the fabric is coated on both sides with collagen fibrils.

6. A device according to any of claims 1—5 in which the fabric is in the form of a tube.

7. A device according to claim 6 in which the tube carries a plurality of reinforcing rings spaced apart axially, the rings being of a material non-absorbable by the body fluids.

8. A device according to claim 6 in which the tube carries a reinforcing helix of a material non-absorbable by the body fluids.

9. A device according to any of the preceding claims in which the fabric is woven, knitted, crocheted, or braided.

10. A device according to claim 9 in which the fabric is tulle.

11. A device according to any of the preceding claims in which the fabric is formed from yarns of a synthetic organic resinous compositions.

12. A device according to any of claims 1—10 wherein the fabric is formed from any of the materials hereinbefore specifically mentioned.

13. A device according to any of the preceding claims comprising a fabric formed from strands of material non-absorbable by the body fluids, and collagen strands.

14. A device according to claim 13 in which the collagen strands are multifilament strands.

15. A surgical device constructed and arranged substantially as hereinbefore described and shown in Fig. 1 and 2, or, 3, 3a, and 3b, or Fig. 4, or Fig. 5 of the accompanying drawings.

16. A method of manufacturing surgical prostheses which comprises the steps of:

impregnating a fabric non-absorbable by fluids present in the human or animal body with an aqueous acid dispersion of swollen collagen fibrils,

freezing the aqueous acid dispersion of swollen collagen fibrils,

immersing the frozen mass in a water-miscible organic solvent containing sufficient base to neutralize the acid present in said dispersion,

removing the resulting structure from the organic solvent and,

drying the resulting structure.

17. A method according to claim 16 wherein the fabric is produced by knitting or weaving.

18. A method according to claims 16 or 17 wherein the solvent employed is acetone and the base employed is ammonium hydroxide.

19. A method of manufacturing surgical prostheses which comprises weaving, knitting, crocheting, or braiding together collagen multifilament yarn and yarn non-absorbable by fluids present in a human or animal body.

20. A method according to claim 19 in which the said non-absorbable yarn is formed from a synthetic yarn made from terephthalic acid and ethylene glycol.

21. A method of manufacturing surgical prostheses substantially as described in any of the foregoing Examples.

22. A method of manufacturing surgical prostheses substantially as hereinbefore described.

23. Surgical prostheses whenever produced by a method according to any of claims 16—19.

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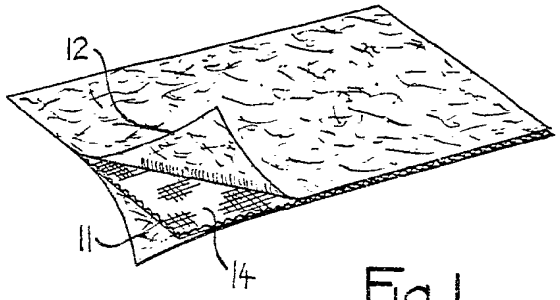

Fig.1.

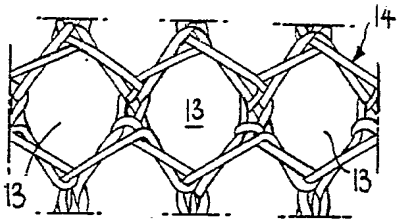

Fig.2.

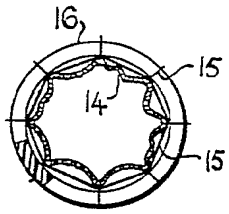

Fig.3a

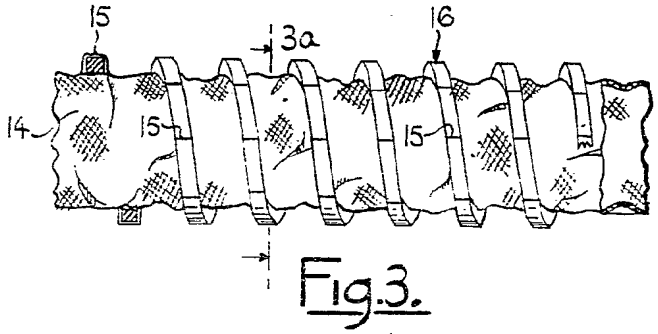

Fig.3.

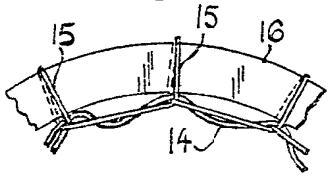

Fig.3b.

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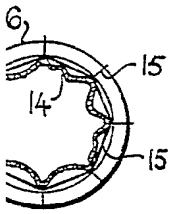

Fig. 3a

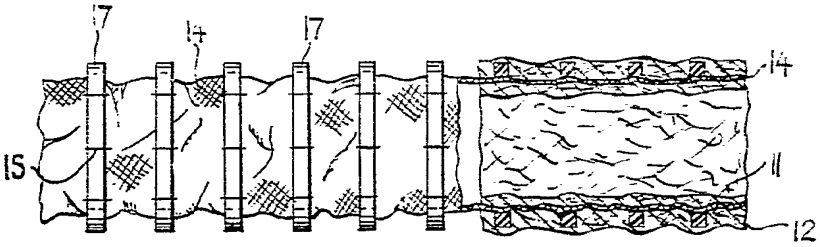

Fig. 4.

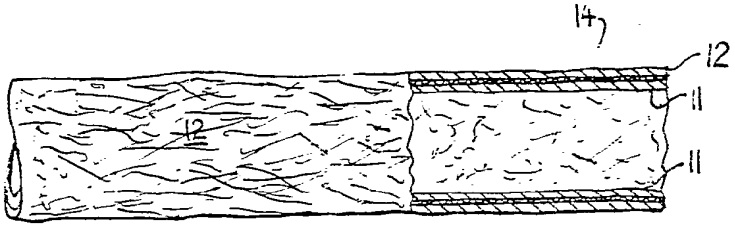

Fig. 5.

Fig. 3b.

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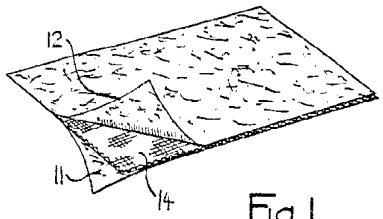

Fig. 1.

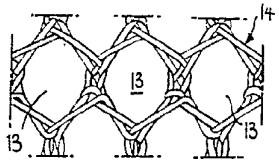

Fig. 2.

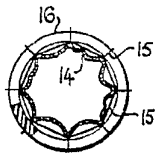

Fig. 3a

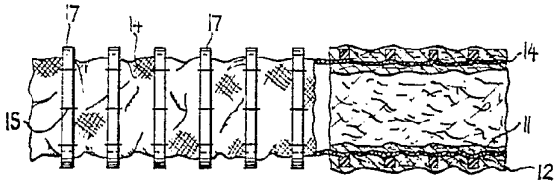

Fig. 4.

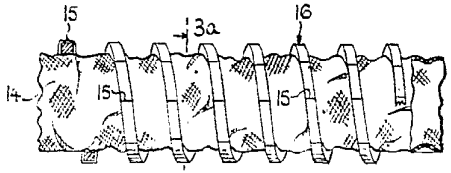

Fig. 3.

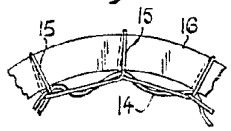

Fig. 3b.

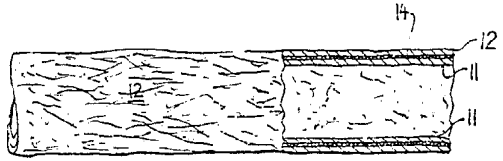

Fig. 5.